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ORIGINAL PAPER

QSPR modeling of thermal stability of nitroaromatic compounds: DFT *vs.* AM1 calculated descriptors

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Abstract The quantitative structure-property relationship (QSPR) methodology was applied to predict the decomposition enthalpies of 22 nitroaromatic compounds, used as indicators of thermal stability. An extended series of descriptors (constitutional, topological, geometrical charge related and quantum chemical) was calculated at two different levels of theory: density functional theory (DFT) and semi-empirical AM1 approaches. Reliable models have been developed for each level, leading to similar correlations between calculated and experimental data (R^2>0.98). Hence, both of them can be employed as screening tools for the prediction of thermal stability of nitroaromatic compounds. If using the AM1 model presents the advantage to be less time consuming, DFT allows the calculation of more accurate molecular quantum properties, *e.g.*, conceptual DFT descriptors. In this study, our best QSPR model is based on such descriptors, providing more chemical comprehensive relationships with decomposition reactivity, a particularly complex property for the specific class of nitroaromatic compounds.

Keywords Density functional theory (DFT) · Nitroaromatic compounds · Semi-empirical calculations · Quantitative structure-property relationship (QSPR) · Thermal stability

Introduction

Quantitative structure-activity and quantitative structure-property relationships (QSAR/QSPR) constitute, nowadays and since many years, very popular computational approaches. Their development, firstly dedicated to biological applications (through the work of Hans [1]), has been promoted for their use as screening tools notably in pharmaceutics [2, 3]. Up to now, most applications of this method concerned biology [4, 5] or toxicology [6, 7], but an increasing interest is now observed for the development of models to predict physico-chemical properties [8–14]. The principle consists in finding relationships between experimental properties and the molecular structures for a set of chemical compounds. Various data mining tools are commonly used: genetic algorithms [15], artificial neural networks [16] or standard statistical tools. Once this model is validated, it is used to predict the properties of compounds with similar structures but it can also be a tool to understand how the structure influences the studied phenomena [17].

If one point of interest is the way to compute models, another fundamental problem concerns the description of molecular structures. In this context, a large number of descriptors has been developed to describe these structures from different points of view (constitutional, topological, electronic...). In particular, quantum chemical approaches appear to be very useful tools, notably for QSPR studies [18]. However, it is important to pay attention to the different levels of theory. Semi-empirical calculations have

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been often employed for the prediction of various properties and compounds [19–24] and many papers recently presented warnings about such a practice [25]. For instance, a decrease in correlation (0.02–0.04) has been observed for the prediction of n-octanol/water partition coefficients [26, 27] and aqueous solubilities [28–30] when using the semi-empirical AM1 method instead of DFT calculations. Meanwhile, Puzyn and coworkers recommended similar parameterized approaches, *i.e.*, PM6 and RM1 methods, for such kind of properties [31]. Moreover, a particular attention is needed during the structural determination step because subsequent consequences on statistical data may be substantial, as clearly demonstrated by Young et al. [32].

In the present paper, DFT and semi-empirically calculated descriptors have been compared for the development of QSPR models on the thermal stability of a series of nitroaromatic compounds. These compounds are recognized as potentially explosive molecules and, in that way, great interest concerns the prediction of their potential hazards. This is particularly true within the new regulatory framework (REACH and GHS). Besides, this class of substances is considered with particular attention among energetic materials because of their complex decomposition process involving different possible reaction paths [33–35]. For instance, *ortho*-substituted nitrotoluenes present specific decomposition channels [35–38]. The influence of chemical structure was considered by Grewer et al. in the early nineties to predict the thermal stability of chemicals [39, 40]. Since then, few models have been developed to predict the properties of energetic materials [19, 20, 41–43]. QSPR models have been developed in a previous work using more specifically DFT calculated descriptors [44, 45]. The present study consists in the investigation of a more extended set of descriptors from both DFT and semi empirical calculations for the same nitroaromatic compounds.

Methodology

Experimental data

The selection of the experimental data is a critical point in QSPR studies. As properties can be very sensitive to experimental conditions, models have to be developed from training values obtained by following a unique protocol in the same conditions. In our work, decomposition enthalpies (-ΔH) were extracted from a single reference [46] to characterize the thermal stability of 22 nitroaromatic compounds. These data were obtained with the same experimental protocol from differential scanning calorimetry (DSC). They are presented in Table 1.

Computational details

All molecular structures were determined using the Gaussian03 quantum chemical package [47]. Optimized structures and vibrational frequencies were computed at the DFT level using the parameter free PBE0 functional [48] and the 6–31+G(d,p) basis set, including diffuse functions on heavy atoms. All structures have been checked to present no imaginary vibrational frequency. Semi-empirical optimizations have also been carried out with the Austin method 1 (AM1) parameterization [49].

Molecular descriptors

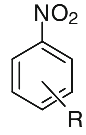
Up to 300 molecular descriptors have been calculated using the CodessaPro software [50] starting with the DFT and AM1 optimized structures. These descriptors can be divided into several classes: constitutional, topological, geometrical, quantum chemical and charge-related descriptors. Their detailed definitions as well as supplementary information can be found in Ref. [18].

Constitutional descriptors are related to the number of specific types of atoms and bonds in the molecule (*e.g.*, number of O atoms, of single bonds *etc*...). Topological ones characterize the atomic connectivities in a molecule including information about the size, composition and degree of branching of the molecule from its hydrogen-suppressed 2D-structure (*e.g.*, Wiener index). Geometric descriptors stem from the 3D-structure (*e.g.*, molecular volume). Quantum chemical descriptors provide information about binding, formation, molecular orbital energies, partial atomic charges and the total dipole moment. Finally, charge-related descriptors characterize the charge distribution in the molecule (partial charges, polarity parameter, charged partial surface areas *etc*...).

Statistical analyses

All statistical analyses have been performed with CodessaPro including notably linear and multilinear regressions. An important point in QSPR analysis is the determination of the best set of descriptors in the final model chosen among the initial set. To achieve this goal, we employed the "best multi linear regression" method (BMLR). The first step of this method consists in the reduction of the number of descriptors by eliminating those which present an insignificant variance or correlation with the studied property. When two descriptors are highly correlated together, the one presenting the lower correlation with the property is also eliminated. Therefore, the two-parameter regressions involving orthogonal descriptors were computed and the best one was selected. Then, orthogonal descriptors were added one by one to select the best models

Table 1 Experimental and predicted decomposition enthalpies (in kJ mol^{-1}) according to the multilinear QSPR models of 22 nitrobenzene derivatives



nitrobenzenes

Compound	Experimental[a]	Previous[b]	DFT[c]	AM1[d]
nitrobenzene	339	333	319	309
1,2-dinitrobenzene	518	599	592	588
1,3-dinitrobenzene	586	498	578	587
1,4-dinitrobenzene	622	701	592	605
2-nitrotoluene	329	356	352	288
3-nitrotoluene	284	322	315	295
4-nitrotoluene	318	306	313	303
2,6-dinitrotoluene	576	497	606	610
3,4-dinitrotoluene	666	571	607	637
2,4-dinitrotoluene	596	493	606	627
2-nitroaniline	307	254	298	316
3-nitroaniline	314	338	309	315
4-nitroaniline	279	218	293	321
2-nitrobenzoic acid	297	473	317	298
3-nitrobenzoic acid	298	378	312	292
4-nitrobenzoic acid	304	452	267	309
2-nitrophenol	345	364	334	322
3-nitrophenol	316	352	324	311
4-nitrophenol	300	275	314	314
1-chloro-4-nitrobenzene	360	368	317	338
2,4-dinitrophenol	662	495	657	662
2,4,6-trinitrophenol	1173	1153	1167	1142
	MAE[e]	65	22	20

[a] from Ref. 46.
[b] based on Eq. 2, corresponding to previous work [44].
[c] based on Eq. 3.
[d] based on Eq. 5.
[e] mean absolute error

at higher ranks. Adding descriptors provides obviously a higher correlation. However, an excess of descriptors leads to over-parameterized models which lose their applicability to molecules outside the training set. For this reason, our models have been developed in order to offer the best compromise between the number of descriptors and the robustness of the regression. Furthermore, a statistical treatment was applied to evaluate the stability and the robustness of these models. More precisely, correlation (R^2), cross-validation $\left(R^2_{cv}\right)$ coefficients, Fisher criterions (F) and squared standard deviation (s^2) have been determined. In addition, the choice of the descriptors was confirmed by performing a student's t-test at a 95% confidence level.

Results and discussion

Thermal stability is a fundamental property of energetic materials. Indeed, determining the amount of energy released during a decomposition process is particularly important since it gives information about chemical reactivity. But up to now, only few structure-property models have been developed to predict it. QSPR type analyses have been carried out for specific thermal decomposition properties of chromophores and polymers by Figueiredo [51] and Yu [52] respectively. For ionic liquids, Kroon and coworkers [53] proposed the estimation of their decomposition temperature based on the activation energies of the most likely thermal degradation reaction, calculated at DFT level.

In the framework of energetic materials, some trends have been demonstrated linking the decomposition temperature to the molecular composition [39] or to the weak bond dissociation energies [33] of potentially explosive compounds. To our knowledge, Saraf et al. [54] proposed the first QSPR type analysis of the thermal stability properties of nitroaromatic compounds. In this last study, the decomposition enthalpy (-ΔH) was estimated from the number of nitro groups in the molecule (n_{NO2}).

$$-\Delta H\left(kcal\ mol^{-1}\right) = 75 \times n_{NO2} \tag{1}$$

An average error of about 8% can be associated to this. More recently, Keshavarz also proposed two predictive models for the prediction of the activation energy of thermolysis of nitroaromatics and nitramines based on constitutional descriptors with substantial correlations (R^2=0.87) [55, 56].

In previous works, models based on selected DFT calculated descriptors were proposed to predict the decomposition enthalpy of 22 nitrobenzene derivatives [44]. The decomposition of nitro compounds is commonly considered to be initiated by the breaking of the weakest C-NO_2 bond [33]. However, other mechanisms can initiate the decomposition process of nitroaromatic compounds [35], *e.g.*, o-nitrotoluene derivatives [38]. Furthermore, in Ref. [44], the C-NO_2 bond dissociation energies (ΔE_{diss}) did not correlate with experimental decomposition enthalpies (R^2= 0.42). The addition of descriptors arising from the conceptual density functional theory led to significantly correlated models. These global descriptors of reactivity represent a simple way to rationalize the different chemical behavior of similar species. In particular, a reliable three parameter model was proposed (R^2=0.85).

$$-\Delta \mathrm{H}\left(\mathrm{kcal\ mol}^{-1}\right) = -16.9\ \mathrm{EA} + 18.1\ \omega - 3.6\ \Delta \mathrm{E}_{\mathrm{diss}} + 263.8 \tag{2}$$

where EA and ω are the electron affinity and the electrophilicity index respectively. The accuracy of this model reveals the pertinence of using chemical comprehensive descriptors, which characterize the reactivity of the studied compounds without the full characterization of the whole decomposition process.

In the present study, an extended set of descriptors (detailed in section 2) was investigated. The descriptors, computed from both DFT and AM1 optimized structures were integrated into the BMLR method in order to determine the more reliable model available for each calculation level. During this analysis, equations were built consecutively with different numbers of descriptors (up to 7 and 9 descriptors for the analyses using AM1 and DFT calculated structures respectively). Then, an important step concerned the definition of the optimal number of descriptors in the final model to ensure a good robustness without any over-parameterization. In this paper, a threshold value for the improvement in R^2 over the number of descriptors was considered.

In Fig. 1, we present the R^2 correlation coefficients of the models provided by the BMLR method both for DFT and AM1 calculated descriptors. Choosing a threshold value of 0.01 consists in increasing the number of descriptors in the model until R^2 increases by less than 0.01. For DFT calculated descriptors, the increase in R^2 becomes less than 0.01 between the models with three and four descriptors (ΔR^2=0.007). This threshold value can be considered as a reasonable choice since it corresponds to a "breaking point" in the increasing of the correlation over the number of descriptors. Therefore, a three-parameter equation is most predictive DFT model preventing among any over-parameterization and it can be justified when comparing to the four-parameter one.

The three-parameter equation (see also Table 2) is the following.

$$-\Delta \mathrm{H}\left(\mathrm{kJ\ mol}^{-1}\right) = 401.61\ \mathrm{n_N} + 2092.2\ \mathrm{BO_{avg,N}} + 13287\ \mathrm{E_{O,max}} - 3148.5 \tag{3}$$

Descriptors are chemical comprehensive and can be linked to the decomposition process in nitroaromatic compounds. On the one hand, the number of nitrogen

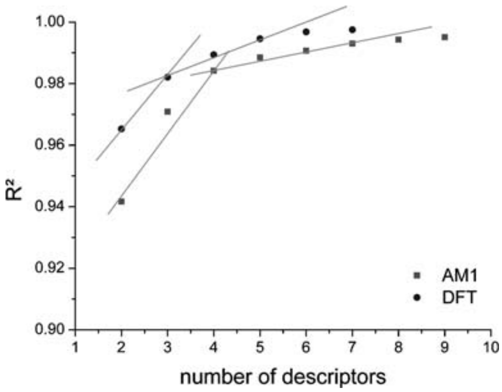


Fig. 1 Number of descriptors versus R^2 of the models from DFT and AM1 calculated structures

Table 2 Three-parameter model for the decomposition enthalpy from DFT[a] calculated structures (R^2=0.982; $R^2_{cv} = 0.974$; F=330; s^2= 963.17)

No.	X	±ΔX	t-test	Descriptors
0	−3.15E+03	1.73E+02	−18.24	Intercept
1	4.02E+02	1.38E+01	29.02	Number of N atoms
2	2.09E+03	1.11E+02	18.89	Avg bond order of a N atom
3	1.33E+04	1.76E+03	7.53	Max electroph. react. index for a O atom

[a] at PBE0/6–31+G(d,p) level

Table 3 Four-parameter model for the decomposition enthalpy from DFT[a] calculated structures (R^2=0.989; $R^2_{cv} = 0.984$; F=397; s^2= 605.60)

No.	X	±ΔX	t-test	Descriptors
0	1.78E+03	1.19E+02	14.92	Intercept
1	3.98E+00	2.45E-01	16.21	Wiener index
2	−6.63E+02	6.55E+01	−10.13	Max bond order of a C atom
3	−1.63E+01	2.64E+00	−6.16	Translational heat capacity (300K) / # of atoms
4	6.02E+03	1.48E+03	4.08	FNSA-3 Fractional PNSA (PNSA-3/ TMSA) [Zefirov's PC]

[a] at PBE0/6–31+G(d,p) level

atoms (n_N) is related to the number of nitro groups, which is commonly recognized as an indicator of explosive properties within the safety regulatory framework [57]. On the other hand, the average bond order of a nitrogen atom ($BO_{avg,N}$) and the maximum electrophilic reactivity index for an oxygen atom ($E_{O,max}$) characterize the ability of nitro groups to dissociate from the nitroaromatic molecules. This three-parameter equation gives only small deviations from experimental values, as shown in Table 1 and Fig. 2, and it presents a R^2 value which is close to the best four-parameter one (0.982 *vs*. 0.989, in Fig. 1).

This four-parameter equation (see also Table 3) is the following.

$$-\Delta H\left(\text{kJ mol}^{-1}\right) = 3.98\ W - 663.16\ BO_{max,C} - 16.30C_{v,tr} + 6024.4\ FNSA3 + 1781.3 \qquad (4)$$

In this model, the Wiener index (W), which characterizes the branching degree of molecules, can be interpreted as a degree of substitution of the aromatic ring. The maximum bond order of a C atom ($BO_{max,C}$) is a description of the C-NO_2 bond, the first dissociated group in nitroaromatic compounds. The last two descriptors (the translational heat capacity per atom at 300K, $C_{v,tr}$, and the fractional atomic charge weighted partial negative surface area, FNSA3) are more difficult to interpret. Statistically, these two last parameters are the less significant ones according to the Student's t-test. As shown in Fig. 1, the 3-parameter equation is close to the 4-parameter one from a statistical point of view. Moreover, the interpretation of descriptors is clearer since some of the descriptors chosen in the four-parameter equation are more difficult to link to thermal stability. Then, the three-parameter model can be recommended since it associates chemical comprehensive descriptors while ensuring against any over-parameterization.

A good predictive and chemical comprehensive model has been obtained from DFT optimized structures. In the following, the same analysis has been carried out at a less time consuming level of theory. Semi-empirical calcula-

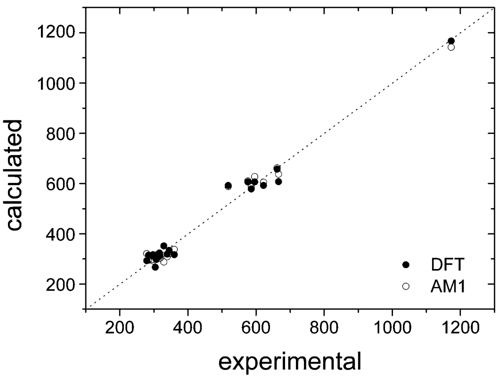


Fig. 2 Experimental versus predicted decomposition enthalpies (in kJ mol^{-1}) according to the models in Tables 2 and 4, in plain and wide circle respectively, dashed line representing an ideal agreement

Table 4 Four-parameter model for the decomposition enthalpy from AM1 calculated structures (R^2=0.984; $R^2_{cv} = 0.967$; F=265; s^2= 901.98)

No.	X	±ΔX	t-test	Descriptors
0	3.05E+03	5.17E+02	5.90	Intercept
1	2.70E+00	1.35E-01	20.05	Wiener index
2	−1.24E+02	2.93E+01	−4.23	Average information content (order 1)
3	−4.39E+03	5.29E+02	−8.30	Max partial charge for a C atom [Zefirov's PC]
4	4.00E+04	8.05E+03	4.97	Max partial charge for a O atom [Zefirov's PC]

tions have been considered for the calculation of descriptors for the prediction of various physico chemical properties [13, 14]. In particular, Katritzky considered AM1 calculated descriptors in QSPR models for the flash point [19, 20]. So the pertinence of this level of theory was investigated for the thermal stability of our nitroaromatic compounds.

On Fig. 1, it has to be remarked that, for each number of descriptors, AM1 models present smaller correlations than the DFT ones. The optimal number of descriptors is determined to be a four-parameter one.

$$-\Delta \mathrm{H} = 2.70\mathrm{W} - 124.03^{1}\mathrm{IC} - 4389.3\ \mathrm{Q}_{\mathrm{C,max}} + 40022\ \mathrm{Q}_{\mathrm{O,max}} + 3050.7 \qquad (5)$$

This model (see also Table 4), is mainly composed of the Wiener index, characterizing the number of substituents. The three other descriptors are less significant (regarding t-test values). The maximal partial charges for C and O atoms, $\mathrm{Q}_{\mathrm{C,max}}$ and $\mathrm{Q}_{\mathrm{O,max}}$, (calculated with Zefirov's empirical method [18]) are expected to be relative to the typical NO_2 group and the average information content index (order 1), $^{1}\mathrm{IC}$, is also expected to encode the branching ratio of the molecule. If this equation is as significantly correlated as the corresponding one based on DFT calculations (R^2=0.984 *vs.* 0.982), it is slightly less predictive regarding cross-validated R^2 (0.967 *vs.* 0.974). Moreover, the descriptors used are less directly related to the decomposition properties of nitroaromatic compounds. All descriptors in the DFT model (Eq. 3) are relative to the NO_2 group whereas the Wiener index and the average information content may be less directly connected to thermal stability. The good correlations observed with AM1 are explained by the fact that the Wiener index and the information content index, the main descriptors in AM1 model, correspond to topological descriptors only based on the "skeleton structure" of the molecule. In particular, the contribution of W in the equation is very important since a simple linear regression already provides a high correlation coefficient with experimental data (R^2=0.81). Moreover, the t-test value of W in Eq. 5 is equal to 20 when, for other descriptors, this value varies between 4 and 8.

Besides, replacing AM1 optimized structures by DFT ones, the same set of descriptors provides a similar model.

$$-\Delta \mathrm{H}\left(\mathrm{kJ\ mol}^{-1}\right) = 2.69\ \mathrm{W} - 122.78^{1}\mathrm{IC} - 4406.7\ \mathrm{Q}_{\mathrm{C,max}} + 40652\ \mathrm{Q}_{\mathrm{O,max}} + 3091.1 \qquad (6)$$

This new relationship leads to an identical correlation with R^2=0.984. Nevertheless, the above mentioned BMLR analysis (leading to Eq. 3) favors chemical comprehensive descriptors with a higher Fisher criterion (F=330 *vs.* 266).

Conclusions

A quantitative structure-property relationship study has been realized for the decomposition enthalpy of 22 nitroaromatic compounds in order to find correlations with their molecular properties. An extended set of more than 300 descriptors (constitutional, topologic, geometric, charge related, quantum chemical) was computed from both semi-empirical (AM1) and ab initio (DFT) calculated structures.

For each level of theory, statistically significant models were obtained using a best multilinear regression analysis with quite similar correlations (R^2=0.98). However, the set of descriptors used by the DFT model is more directly connected to thermal stability property than the AM1 one. DFT model corresponds to a three-parameter equation in which three descriptors appear to be related to the number and reactivity of nitro groups whereas the four-parameter AM1 model is mainly based on the pure topological Wiener index, characterizing here the degree of substitution of the aromatic molecules.

Finally, semi-empirical model gives a sufficient high correlation and seems adequate as a simple screening tool. Indeed, the good correlation observed for the AM1 model is due to the good correlation of the simple topological Wiener index with experimental values that do not need any advanced level of theory. However, density functional theory offers a better accuracy in the estimation of quantum descriptors. To the end, the DFT model ensures a similar high reliability and, furthermore, includes more chemically sound descriptors.

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